DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
New Orleans District Office
6600 Plaza Drive, Suite 400
New Orleans, LA 70127

July 2, 2001

Via Federal Express

Mr. Michael L. Essay, President
Meridian Pharmaceuticals, Inc.
1316 Commerce Drive NW
Decatur, AL 35601

Warning Letter No. 01-NSV-35

Dear Mr. Essay:

This letter is in reference to an inspection of your firm conducted on February 21-22 and March 5-7, 2001 by an investigator of the Food and Drug Administration. The inspection disclosed that your firm receives active pharmaceutical ingredients and subsequently repackages and relabels these for further distribution to pharmacies for compounding of drug products.

The inspection revealed significant deviations from current good manufacturing practice in the repacking and relabeling of active pharmaceutical ingredients (APIs). These deviations cause the APIs to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed and held according to current good manufacturing practice (CGMP). No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have reviewed your firm's letters dated April 10, 2001, May 7, 2001 and May 24, 2001, from Mr. David Adsit, Materials Manager, concerning our recent inspection of your firm. We also acknowledge our meetings and telephone conversations with your firm concerning the observations listed on the March 7, 2001, FDA 483, issued to your firm.

We feel that your firm has not promised adequate corrections to many of the significant CGMP deviations observed during our February 21-22 and March 5-7, 2001, inspection of your firm. These deviations include, but are not limited to:

1. Failure to demonstrate the adequacy of the expiration dating assigned to the APIs that are repackaged by your firm. Your firm routinely assigned to your repackaged APIs the same expiration dates provided by your API suppliers on their container labels or certificates of analysis. There was no assurance that the expiration dates assigned to your repackaged APIs were appropriate because there were no data to demonstrate equivalence of the container-closures used by your firm with the original container-closure systems used by your suppliers of the APIs. Additionally, in the absence of any container-closure equivalency data, there was no stability data to support the validity of the expiration dating assigned to your repackaged APIs.

Your response to the FDA 483 does not adequately address the issue of assigning appropriate expiration dating to your repackaged APIs. Your response states that the expiration dating placed by your firm on the repackaged containers is not based on stability studies, but rather on the expiration dating on the manufacturers' containers from which the APIs are repackaged. You assert that it is acceptable to assign the manufacturers' expiration dates to the corresponding repackaged APIs because "the containers are either the same type or superior to the original in which the manufacturer placed the product." You further state that APIs received by your firm in glass or plastic containers are also repackaged into glass or plastic containers.

Considering the many different types and grades of glass and plastic containers, merely repackaging into a glass or plastic container whose properties are unknown gives no assurance that the containers are equivalent or that the container used for repackaging is appropriate for the repackaged API. Your response indicates that your firm does not have any sound justification for considering your container-closures equivalent to or superior to the protective properties of the original container-closures used by your suppliers from which you obtain your repackaged API expiration or retest dating.

Your batch records for each repackaged API should include a complete description of the original container-closure system in which the API is received from your supplier, the new container-closure system used for repackaging, and your justification for any determination made concerning the comparability or equivalency of the containers. As mentioned, such justification should include scientifically sound data demonstrating the equivalency of the container-closure systems.

It also is your responsibility to ensure that the container-closure systems used for repackaging APIs are compatible with the APIs in that they are not reactive, additive or absorptive so as to adversely alter the safety, identify, strength, quality or purity of the API. We are especially concerned about the lack of any assurance of compatibility of container-closures used with liquid APIs that are repackaged by your firm.

2. Failure to assign an expiration or retest date to numerous APIs that are repackaged by your firm.

Our inspection found that numerous APIs repackaged by your firm were released and distributed without any expiration or retest dating. It appears that your firm received many of these APIs without any expiration or retest dating from your API suppliers. However, our inspection also noted numerous instances in which your API suppliers furnished an expiration or retest date on their certificates of analyses, yet no expiration or retest date was assigned to the same APIs repackaged by your firm. Consequently, there is no assurance that such APIs repackaged and distributed by your firm will not be used for the preparation of finished drug products beyond the time that they will meet all of their appropriate specifications.

Your firm's response to FDA 483, observation 3, states that your policy will be reviewed concerning the assigning of expiration or retest dating taken from certificates of analyses, and that there will be retraining to ensure that proper procedures are followed. Your response however, does not state what actions your firm will take to ensure that appropriate expiration

or retest dating is assigned to APIs that your firm repackages in instances in which your API suppliers do not furnish any expiration or retest dating.

3. The expiration date assigned by your firm to repackaged Capsaicin, USP, lots 01170101 and 01170102, was "05/2003," yet your supplier's certificate of analysis for the same lots had an expiration date of "5/2000." Additionally, your firm labeled the repackaged lots as synthetic capsaicin even though the manufacturer's certificate analysis identified the API as natural capsaicin.

   Your firm's response to FDA 483, observation 9, states that your vendor typed its certificate of analysis for "Capsaicin, USP, Synthetic," incorrectly, and when presented with the conflicting information, your vendor verified the information on the original manufacturer's certificate of analysis. You state that your vendor's corrected certificate of analysis sent to your firm has an expiry date of 05/2003. You make no mention as to whether the corrected certificate of analysis identifies the API as synthetic or natural capsaicin.

   Your FDA 483 response does not include a copy of the original manufacturer's certificate of analysis or your vendor's corrected certificate of analysis referred to in your response. Please provide us with a copy of the corrected certificate analysis and the date that your firm received it.

4. Failure to have drug product, container-closure and master label specifications for each drug that your firm repackages. Your firm also lacks procedures showing that APIs, labels and container-closures are examined to ensure that they meet appropriate specifications prior to their use in repackaging operations.

   For example, your firm's batch records for repackaged Dimethyl Sulfoxide (DMSO), lots 00310801 and 00310802, indicate that the repackaged lots were labeled as "Dimethyl Sulfoxide, USP." However, your supplier's certificate of analysis for the same lots states that the product is an industrial grade of DMSO, and makes no claim that the lots comply with USP specifications.

   Our inspection also noted that there are no master labels and the drug names were spelled incorrectly on some drug labels placed by your firm on repackaged drug products.

   Our inspection noted that APIs in powder and liquid form are repackaged into different types and sizes of containers. Your firm lacked specifications for the different types of containers, and lacked any procedures or specifications showing which APIs were suitable for packaging into each different type of container-closure used by the firm.

   You responded that new specifications and acceptance procedures would be established but did not provide us with any examples of the new procedures that you plan to implement. Therefore, we are unable to evaluate the adequacy of your response. We will verify your implementation of the new specifications and procedures that you promise during our next inspection

5. Failure to have written procedures (SOPs) for some significant aspects of your repackaging operations and failure to follow certain of your written SOPs.

For example, there are no procedures for maintaining temperature and humidity control in the repackaging rooms. We are especially concerned about the lack of any procedures to control humidity in areas that repackaging is conducted for APIs that may be moisture sensitive.

Your firm failed to follow its written SOPs for cleaning repackaging areas, for documenting weekly calibration of the scales used to weigh raw materials during repackaging operations, and for maintaining reserve samples of repackaged drugs.

You state in your response that SOPs have been updated to reflect your current repackaging operations. Your response appears to be adequate, but as above, you did not include with your response any examples of your updated procedures. We will verify your response during the next inspection.

The above violations are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that all your drug products are in compliance with the Act and its implementing regulations. Federal agencies are advised on the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

We request you take prompt action to correct these violations. Failure to promptly correct these violations may result in enforcement actions being initiated by the Food and Drug Administration without further notice. The Federal Food, Drug, and Cosmetic Act provides for the seizure of illegal products and for injunction against the repacker and distributor of illegal products.

Please notify this office in writing within fifteen (15) working days of receipt of this letter as to the specific steps you have taken to correct the stated violations, including an explanation of each step being taken to identify and make corrections to assure that similar violations will not recur. If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the corrections will be implemented.

Your reply should be sent to the attention of Joseph E. Hayes, Compliance Officer, Food and Drug Administration, 297 Plus Park Boulevard, Nashville, TN 37217.

Sincerely,

Carl E. Draper

Carl E. Draper
Director, New Orleans District

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